

Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



December 3, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry on Handling and Retention of Bioavailability and Bioequivalence Testing Samples [Docket No. 02D-0350, 67 *Federal Register*, 54219, August 21, 2002 and 67 *Federal Register*, 64401, October 18, 2002]

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than \$30 billion in 2001 in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

We welcome the opportunity to comment on the draft guidance on the handling and retention of bioavailability and bioequivalence testing samples and appreciate the extension of the deadline to do so. We trust that you will give careful consideration to our attached comments as you finalize the guidance.

Please feel free to contact me if you have any questions.

Sincerely,

A handwritten signature in cursive script that reads 'Alice E. Till'.

Alice E. Till, Ph.D.

CC M. Yau

Att.

02D-0350

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Pharmaceutical Research and Manufacturers of America

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Final Comments on FDA Draft Guidance for Industry: Handling and Retention of BA and BE Testing Samples

General Remarks

We generally agree that this guidance will clarify the procedures and requirements for handling reserve samples from relevant bioavailability (BA) and bioequivalence (BE) studies. However, this guidance, intended to aid study sponsors and/or drug manufacturers, seems to place additional burdens on sponsor run facilities. **Section IV, D - Studies Conducted *In-House* by a Study Sponsor and/or Drug Manufacturer** (beginning line 337) describes additional controls for in-house facilities that are not required for contractor commercial operations including the use of third parties and independent third parties to witness dosing. It is not clear what value these would add and what the rationale is for these additional requirements for sponsor testing facilities as opposed to commercial or contract testing facilities.

Specific Comments

Line 258 Section IVB., Studies Involving SMOs

Comment: This portion of the guidance appears contradictory and may actually lead to the very situation that the regulation was intended to prevent, i.e., the manipulation of study samples and/or data due to the potential for an SMO to increase its compensation. In the first instance, line 279 states that “The SMO should *not* select and retain reserve study samples”. However in line 281, it states, “if one or more of the testing facilities do not have an adequate storage facility, reserve samples can be transferred back to the SMO for storage.” The guidance is inconsistent as it both recommends against retaining reserve study samples at the SMO, and as it also allows this if the test facility has inadequate storage. We suggest the former position (SMO should not retain the reserve study sample) for the reason that SMO’s are not explicitly recognized as an entity in another FDA regulation, 21CFR Part 54, Financial Disclosure for Clinical Investigators, which was developed to address the potential for bias on the part of clinical investigators. In Part 54, sponsors are required to disclose any payments made to clinical investigators in terms of stocks or stock options, actions which the FDA has stated may bias their reporting (favoring the sponsor’s product), as good news on a clinical trial may positively effect the value of the stocks or options held by the them. We are not aware that any certification by an applicant for financial disclosure is required if stock or stock options were used to compensate an SMO who is retaining reserve samples. As stated in the Background section of this guideline, the FDA issued the rule on retention of BA and BE testing reserve samples in response to the generic drug scandal in the 1980s. By allowing SMOs to retain reserve samples, the agency could be recommending the establishment of an environment that could increase the potential for introducing bias into the process, and yet not be aware of those instances where SMOs were compensated by other than fee for service.

Comment: Throughout the document there appears to be this notion that multi-center trials must involve an SMO and cannot be run by sponsor.

Line 339 Text: It is uncommon for study sponsors and/or drug manufacturers to conduct BA/BE studies in their own facility.

Comment: For study sponsors and/or drug manufacturers who have clinical trials/studies/pharmacology units operating within their clinical R&D organizations, it is reasonable and appropriate to carry out BA/BE investigations at these facilities. To state otherwise is to imply an element of impropriety about the practice that is not warranted. Therefore, we recommend that this sentence be deleted.

Line 347 Text: To preclude any potential appearance of possible substitution, it would be prudent for study sponsors and/or drug manufacturers to remove themselves from reserve sample selection and retention. It is recommended that the firm engage a third party for retention of reserve samples.

Comment: It is our belief that BA and BE studies may be conducted by in-house clinical pharmacology units, given the proper written procedures for how samples are selected, identified, and stored, along with conditions of storage and access to the materials. The recommendation in the draft guideline is excessive and would increase the cost of the research process without adding commensurate value. Further, each transfer of samples to a third party puts the samples at risk for mishandling. There are also potential issues regarding confidentiality and other security concerns with shipping these supplies to external vendors. The FDA has not adequately explained or justified to the research based industry why these recommendations would improve compliance.

As an alternative option, the guidance could provide a linkage to other means by which the sample retention obligations could be satisfied. For example, suppose the sponsor has a totally separate and fully compliant house sample storage facility, with process, procedure and policy in place whereby adequate samples are retained from every lot of manufactured drug product. If this process also includes a rigorous chain of custody and linkage to drug product labeling and identity, and linkage to drug product used in specific studies, such a system could obviate the need for a separate and specific BE study sample retention.

Finally, the draft guidance contains inconsistent text in lines 349 and 367 regarding third party sample retention. Line 349 states that a 3rd party is recommended while line 367 states that a third party is advised.

Line 361 Text: It is recommended that an independent, third party be available to witness dosing and random selection of reserve samples.

Comment: "Independent" requires clarification and more definition. Could part-time contractors or hospital employees serve as an independent third party if that is being required by FDA? If the independent third party is receiving compensation from the sponsor or clinical site is he or she truly independent? The terminology "be available" also is open to interpretation. Does FDA want to mandate a role for in-house studies when such a role is not mandated for studies conducted at a CRO? Engaging a third party to witness dosing and random selection of reserve samples would cause additional costs in hiring these witnesses, as well as possibly delaying

research if the unit is ready to dose and the independent witness is unavailable for a variety of reasons.

Lines 363 through 368 Text: Reserve samples should be retained in a secure room in the clinical study unit. To protect the study sponsor or drug manufacturer from challenge to the authenticity of the reserve samples, access to the room where samples are stored should be limited to the clinical investigator or research pharmacist. An entry log to the storage room should also be maintained. It is advised that an independent, third party be used for retention of reserve samples.

Comment: As a practical matter, such a room would clearly be under the control of the study unit or other sponsor staff. How is this statement to be reconciled with the content of lines 349 and 367-368? The text is needlessly prescriptive. We suggest, "Reserve samples should be retained in a secure room. To protect the study sponsor or drug manufacturer from challenge to the authenticity of the reserve samples, access to the room where samples are stored should be limited. An entry log to the storage room should also be maintained. If the testing facility does not have an adequate storage facility, or goes out of business, the reserve samples can be transferred to an independent, third party with an adequate facility for storage under conditions consistent with product labeling."

Line 438: Text: **Site Management Organization (SMO)**

Comment: There appears to be some confusion regarding the definition of SMO and CRO. This document identifies SMO as a CRO. However, an SMO would only be a CRO if the sponsor transferred some of their obligations under IND to the SMO. Typically SMOs do not assume sponsor obligations but provide administrative and logistical support for a study. Even when SMOs have investigators that are available to a sponsor, only in the unlikely event that the sponsor allows the selection of investigators by the SMO would they be considered to be a CRO. The services they usually provide are those that an investigator would perform such as supplying, study coordinators, completing case report forms, etc.